Relationship between neuropsychiatric disorders and cognitive and behavioural change in MND

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Objective: In this population-based study, we aimed to determine whether neuropsychiatric history, medication or family history of neuropsychiatric disorders predicted cognitive and/or behavioural impairment in motor neurone disease (MND).

Methods: People with MND (pwMND) on the Scottish CARE-MND register, diagnosed from January 2015-January 2018, with cognitive and/or behavioural data measured using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) were included. Data was extracted on patient neuropsychiatric, medication and family history of neuropsychiatric disorders.

We identified patients with cognitive (MNDci, MNDcbi or MND-FTD) and behavioural (MNDbi, MNDcbi or MND-FTD) impairment.

Results: Data were available for 305 pwMND (mean age at diagnosis=62.26 years, SD=11.40), of which 60 (19.7%) had a neuropsychiatric disorder. A family history of neuropsychiatric disorders was present in 36/231 (15.58%) of patients.

Patient premorbid mood disorders were associated with increased apathy (OR=2.78, 95%CI=1.083 to 7.169). A family history of any neuropsychiatric disorder was associated with poorer visuospatial scores, MNDbi (OR=3.14, 95%CI=1.09 to 8.99) and MND-FTD (OR=5.08, 95%CI=1.26 to 20.40). A family history of mood disorders was associated with poorer overall cognition (exp(b)=0.725, p=0.026), language, verbal fluency and visuospatial scores, and MND-FTD (OR=7.57, 95%CI=1.55 to 46.87). A family history of neurotic disorders was associated with poorer language (exp(b)=0.362, p<0.001), visuospatial scores (exp(b)=0.625, p<0.009) and MND-FTD (OR=13.75, 95%CI=1.71 to 110.86).

Conclusions: Neuropsychiatric disorders in patients and their families are associated with cognitive and behavioural changes post-MND diagnosis, with many occurring independently of MND-FTD and C9orf72 status. These findings support an overlap between MND, FTD and neuropsychiatric disorders, particularly mood disorders.

Up to 50% of people with amyotrophic lateral sclerosis (ALS), the most common form of motor neurone disease (MND), experience cognitive and/or behaviour changes, with 15% meeting the criteria for frontotemporal dementia (FTD).[1, 2] These changes represent a range of frontotemporal spectrum disorders in ALS (ALS-FTSD).[3] A genetic and pathological overlap between MND and FTD has been established with the C9orf72 repeat expansion occurring in ~6.3% of sporadic ALS cases, ~5.8% of sporadic FTD cases[4] and ~33% of familial MND cases,[5] and the TAR-DNA-binding protein 43 (TDP-43) occurring in almost all ALS, ALS-FTD and ~45% FTD cases.[6-8]

Cognitive and behavioural symptoms in MND range from no impairment to cognitive impairment (ALSci), behavioural impairment (ALSbi), both (ALScbi) or ALS-FTD.[3] An association between neuropsychiatric disorders and ALS has previously been shown.[9, 10] Neuropsychiatric symptoms including schizophrenia, depression, anxiety and drug abuse or dependence are common in the years prior-to and following diagnosis in both ALS[10, 11] and behavioural variant FTD.[12] Genome wide association studies (GWAS) have revealed a modest genetic correlation between schizophrenia and ALS.[13] Furthermore, higher rates of psychosis, suicidal behaviour [14] and autism[15] have been shown in ALS patients' first and second-degree relatives,[14, 15] particularly in their children.[11] Despite evidence of an overlap of ALS-FTSD and neuropsychiatric disorders, it is unclear if neuropsychiatric disorders also contribute to the spectrum of cognitive and behavioural changes in ALS.

Using population-based data from the Scottish Clinical, Audit, Research and Evaluation of MND (CARE-MND) register, this study aimed to look at the association between cognitive and/or behavioural changes in MND as measured using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)[16] and neuropsychiatric disorders in MND kindreds'. Specifically, we aimed to determine if the presence of cognitive and behaviour changes can be predicted by the patient's:

1. History of neuropsychiatric disorders
2. History of neuropsychiatric medication
3. Family history of neuropsychiatric disorders.

METHODS

Participants:

We studied people with MND (pwMND) registered on the CARE-MND platform, a population-based, prospective database of patients in Scotland diagnosed with MND.[17, 18] Since 2015, a major update of the register has taken place. Ethical approval was obtained for the original (MREC/98/0/56 1989-2010, 10/MRE00/78 2011-2015) and updated CARE-MND platform (Scotland A Research Ethics Committee, 15/SS/0126). Anonymised data for collaboration can be obtained upon reasonable request from the CARE-MND register. In Scotland, any patient receiving a diagnosis of MND (including ALS, and subtypes such as primary lateral sclerosis (PLS), progressive muscular atrophy (PMA) and progressive bulbar palsy (PBP)) is included on the register. pwMND can consent for their anonymised information to be used for research purposes. This study includes all consenting patients diagnosed with MND (240 ALS, 23 PLS, 9 PMA and 23 ALS-FTD) between January 2015 to January 2018 with ECAS data available.

Measures:

History of neuropsychiatric disorders

Neuropsychiatric history in patients:

We identified patients with a history of neuropsychiatric disorder (pre- or post-MND diagnosis) from data on the CARE-MND register, using medical history information. We assessed each patient on a case-by-case basis, and identified any relevant neuropsychiatric diagnoses (Table 1). Each diagnosis was then categorised based on the International Classification of Diseases–10 (ICD-10). [19] We created a summary variable to indicate (yes/no) the presence of a relevant neuropsychiatric diagnosis for each individual.

Table 1. Neuropsychiatric disorders of MND patients on the CARE-MND register.

ICD 10 Classification	Neuropsychiatric disorder reported on CARE-MND Register
Mood [affective] disorder F30-F39	Depression Low mood Neurotic (reactive) depression Mania
Neurotic, stress-related and somatoform disorders F40-F48	Anxiety Claustrophobia Obsessive compulsive disorder

	Post-traumatic stress disorder
	Panic attacks
Mental and behavioural disorders due to psychoactive substance use F10-F19	Personal history of psychoactive substance abuse
	Benzodiazepine dependence
	Alcohol excess
	Alcohol abuse
	Referral alcoholic
	Alcohol dependence syndrome
Schizophrenia, schizotypal and delusional disorders F20-F29	Affective psychoses
	Visual hallucinations
Disorders of adult personality and behaviour F60-F69	Personality disorder
Intentional self-harm X60-X84	Suicide + self-inflicted poisoning by solvents

Neuropsychiatric medication history in patients:

We assessed each patient's medication history (pre- and post-MND diagnosis) to identify any relevant neuropsychiatric medication (supplementary eTable 1). We excluded medication typically used to treat the symptoms of MND (e.g. lorazepam) and cases where alternative or secondary use of the medication were stated (e.g. muscle cramps). We created a summary variable to indicate (yes/no) the presence of a relevant neuropsychiatric medication for each individual.

Family history of neuropsychiatric disorders:

Information on a family history of neuropsychiatric disorders (pre-MND diagnosis) was available on the CARE-MND register. These data were collected during routine clinical assessment around the time of MND diagnosis using a standardised proforma. Patients provided information on any family history of MND, dementia, neurological or neuropsychiatric disorders across four generations of blood relatives (patient's grandparents to children). We defined a positive family history as one or more relatives with a diagnosed neuropsychiatric disorder.

Cognition and Behaviour

ECAS cognitive and behaviour scores

Cognition and behaviour were measured using the ECAS.[16] This brief assessment, specifically designed for patients with motor degeneration, is both sensitive and specific to the types of impairments shown by ALS patients[20-23] and is routinely undertaken in Scotland. ECAS subscales are grouped into ALS specific domains (language, verbal fluency and executive functioning) and ALS non-specific domains (memory and visuospatial skills). A total score (max 136) and domain specific scores (ALS-Specific, max 100, ALS non-specific max 36) are calculated with established cut-offs indicating global and domain-specific impairment. The ECAS has been shown to be a sensitive and valid measure of cognition and behaviour in MND[16, 20] with good convergent validity with other screening tests.[21-24]

The ECAS behavioural interview was used to assess behaviour change across five domains based on behavioural-variant FTD diagnostic criteria:[25] disinhibition; apathy or inertia; loss of sympathy/empathy; perseveration and eating behaviour/hyperorality. The interview was completed by an informant, with a score of one indicating a behaviour change for that domain, with a maximum of five denoting the number of behavioural domains affected.

MND-FTSD subclasses

Using all available cognitive and behavioural data, we classified patients using the ALS-FTSD criteria.[3] We used published cut-offs for the ECAS total and ALS-specific scores[16] which have been shown to have maximum sensitivity and specificity to detect cognitive impairment against extensive gold standard neuropsychological assessment.[20] As we included all MND subtypes, we referred to these subclasses as MND-FTSD. Using this method, we identified those with cognitive (MNDci), behavioural (MNDbi) or both cognitive and behavioural impairment (MNDcbi). Cases of MND-FTD were identified on the CARE-MND register based on a diagnosis given by a neurologist during clinical examination.

The number of patients in some MND-FTSD subclasses was small for some analyses. To increase power, we collapsed the categories to identify patients with *any* type of cognitive (MNDci, MNDcbi and MND-FTD) or behavioural (MNDbi, MNDcbi, MND-FTD) impairment.

Patients recruited to the CARE-MND register donated blood or saliva for genetic analysis. C9orf72 genotyping was carried out using polymerase chain reaction (PCR) based on methods previously described.[26]

Statistical Analysis:

Some participants had multiple ECAS scores available from repeat testing (n=39, max=3 entries). We included entries with the most complete data (n=23) and where the date of assessment was available (n=2). In cases where there were two entries within 6 months of each other (n=5), we used the first assessment to avoid potential practice effects.[27, 28] We examined predictors of cognitive and behavioural change in MND and given that these may increase during later stages of the disease,[29] we used the most recent ECAS entry for the remaining cases (n=9).

Dates of neuropsychiatric diagnosis and prescription of medication were available for some, but not all patients on the CARE-MND register. We focussed our analyses on all identified cases to increase statistical power. In addition, we conducted secondary analyses examining only those with confirmed premorbid information based on date of diagnosis or prescription of medication.

We examined the relationships between neuropsychiatric disorders, medication and family history and two outcomes: A) continuous cognitive and categorical (yes/no) behavioural ECAS scores and B) MND-FTSD subclasses, including the presence of *any* cognitive or behavioural impairment. The use of continuous scores increased statistical power to detect effects. However, the use of MND-FTSD subclasses to identify predictors of cognitive and/or behavioural impairments has important clinical implications. For analyses using continuous outcomes, we used linear regression and reverse log transformed ECAS scores where appropriate to avoid violation of normality. Results were back transformed for reporting. We examined the presence of each behaviour change using a series of binomial logistic regressions and MND-FTSD subclass using multinomial regression. For collapsed MND-FTSD subclasses indicating the presence of any cognitive or behaviour impairment, we used binomial logistic regression. Where appropriate, sensitivity analyses were conducted to determine if the associations were driven by MND-FTD cases and whether they remained after controlling for C9orf72 status. All analysis was conducted in R[30] and power calculations were conducted using the pwr package.[31]

RESULTS

Information was available for 305 pwMND with ECAS data (mean age at diagnosis=62.26 years, SD=11.40, Table 2). 211 (69.2%) had complete cognitive and behavioural data, 82 (26.9%) had some cognition only and 12 (3.9%) had behavioural data only. C9orf72 status was available in 259 (84.9%) patients, of which 24 (9.3%) carried disease causing expansions.

Total ECAS scores (n=292, unavailable for one case) ranged from 24 to 132 out of 136 (mean=104.74, SD=18.48) and apathy was the most common behaviour change (68/229, 29.7%, see Figure 1 for frequencies of impairment). A MND-FTSD syndrome was found in 156 (51.1%): MNDci was present in 77 (25.2%), MNDbi in 33 (10.8%) and MNDcbi in 29 (9.5%) patients. MND-FTD was identified in 17 (5.6%) patients based on a neurologist's diagnosis. The remaining 149 (48.9%) patients did not fulfil criterion for cognitive and/or behavioural impairment however, 18 patients were impaired on the ALS non-specific but not the ALS specific subscales. There were no significant differences between those with and without any impairment on demographic or clinical characteristics.

Table 2. Descriptive statistics of MND patients on the CARE-MND register with ECAS data (n=305).

Demographic	Mean/Frequency
Age at symptom onset[a]	60.56±11.45
Age at diagnosis	62.26±11.40
Sex: Male	202 (66.2%)
Handedness:	
Right	232 (89.9%)
Left	23 (8.9%)
Both	3 (1.2%)
Diagnosis:	
ALS/MND	240 (78.7%)
ALS/MND-FTD	17 (5.6%)
PLS	23 (7.5%)
PMA	9 (2.0%)
Other/unknown	16 (5.2%)
C9orf72 Status	
C9+	24 (7.9%)
C9-	235 (77.0%)

Not tested	46 (15.1%)
Disease duration at time of ECAS (days)[b]	411.16±770.94
Deceased	178 (58.4%)

± Mean and standard deviation
[a] Patient self-report of motor symptoms
[b] Number of days between diagnosis and ECAS testing (n=294).

The relationship between patients' neuropsychiatric history and cognition and behaviour

Of the 305 people with ECAS data on the CARE-MND register, 60 patients had a medical history of a neuropsychiatric disorder. Those with and without a neuropsychiatric disorder did not differ on C9orf72 status (x^2=0.098, p=0.755), however those with a neuropsychiatric disorder had a shorter disease duration at the time of ECAS (median=81 days) than those without (median=177 days; W=8458, p=0.005). No relationship was found between disease duration and total ECAS, ALS specific or ALS non-specific scores.

Mood disorders were the most common (n=42) followed by neurotic disorders (n=19), personality disorders (n=3), and schizophrenia, schizotypal and delusional disorder (n=1, Table 3). Based on diagnosis date, 39 had a definite premorbid neuropsychiatric disorder (2 were diagnosed post-MND diagnosis, 19 missing date). Those with a premorbid neuropsychiatric disorder had a shorter disease duration at the time of ECAS compared those without (77 vs 177 days, W=5583.5, p=0.006). There were no other significant differences on demographic or disease characteristics.

Table 3. Frequency of neuropsychiatric disorders in MND patients and their family members on the CARE-MND register.

	MND Patients		**MND Family members**
n(%)	**All neuropsychiatric disorders (n=60)[a]**	**Premorbid neuropsychiatric disorders (n=39)[b]**	**Positive family history (n=36)**
Mood disorders	42 (70.00%)	28 (71.80%)	16 (44.44%)
Neurotic disorders	19 (31.67%)	13 (33.33%)	9 (25.00%)
Schizophrenia, schizotypal or delusional disorder	1 (1.67%)	0 (0.00%)	10 (27.80%)
Disorders of adult personality and behaviour	3 (5.00%)	2 (5.13%)	0 (0.00%)

Mental and behavioural disorders due to psychoactive substance use	0 (0.00%)	0 (0.00%)	3 (8.30%)
Intentional self-harm	0 (0.00%)	0 (0.00%)	3 (8.30%)

NOTE: Percentages are based on the number of people with neuropsychiatric disorders on the CARE-MND register (see n in each header).
[a] Includes all cases of neuropsychiatric disorder regardless of date of diagnosis.
[b] Includes neuropsychiatric disorders with a date of diagnosis prior to MND diagnosis only.

The analyses of ECAS scores revealed that a diagnosis of a mood disorder was associated with poorer language scores but no other specific subscale (Table 4). A diagnosis of any neuropsychiatric disorder was associated with increased likelihood of apathy but no other specific behavioural domain. Examination of each individual neuropsychiatric disorder showed an association between mood disorders and increased risk of apathy. We did not find any other significant associations between patient neuropsychiatric disorders and cognition or behaviour. After excluding MND-FTD cases, these associations were no longer significant. After controlling for C9orf72 status, the association between mood disorders and language scores was no longer significant however all other associations remained.

Table 4. Depression and anxiety associations with ECAS cognitive and behaviour scores.

	Neuropsychiatric disorders at any time point (n=60)					
	Any neuropsychiatric disorder		**Mood Disorders**		**Neurotic Disorders**	
	exp(B)	***p***	**exp(B)**	***p***	**exp(B)**	***p***
Language	0.826	0.114	**0.751**	**0.040**	0.940	0.754
Verbal Fluency	0.895	0.296	0.852	0.192	0.990	0.953
Executive functioning	0.914	0.317	0.903	0.328	1.030	0.844
ALS Specific	*0.900*	*0.231*	*0.869*	*0.166*	*1.039*	*0.795*
Memory	0.938	0.400	0.914	0.308	0.858	0.229
Visuospatial	0.950	0.525	0.962	0.676	1.015	0.908
ALS Non-specific	*0.943*	*0.459*	*0.925*	*0.398*	*0.885*	*0.352*
Total ECAS	*0.910*	*0.231*	*0.882*	*0.168*	*0.990*	*0.939*
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Disinhibition	1.177	0.650 to 4.370	1.621	0.507 to 4.393	0.975	0.051 to 5.642
Apathy or inertia	**2.055**	**1.020 to 4.097**	**2.565**	**1.178 to 5.573**	1.950	0.470 to 7.598
Loss of sympathy or empathy	1.257	0.545 to 2.719	1.409	0.555 to 3.280	1.105	0.161 to 4.758
Perseveration	1.328	0.527 to 3.056	1.336	0.465 to 3.354	1.555	0.047 to 5.521
Hyperorality or altered food preferences	1.047	0.397 to 2.462	0.998	0.319 to 2.604	1.510	0.219 to 6.562

Results in bold indicate a significant association.

In secondary analysis examining those with confirmed premorbid neuropsychiatric disorders only (n=39), the association between mood disorders and apathy remained (supplementary eTable 2). The associations between mood disorders and language scores and any neuropsychiatric disorder and apathy were no longer significant; however, in both cases, statistical power was low (0.34 and 0.16 respectively).

The analyses of MND-FTSD classifications revealed that mood disorders were associated with increased odds of MNDbi vs MND with no impairment (Table 5). This association remained after excluding MND-FTD cases and controlling for C9orf72 status. We did not find any other associations (Table 5 and Figure 2a) including those examining premorbid cases only (supplementary eTable 3 and eFigure 1a).

Table 5. Patient neuropsychiatric disorders and MND-FTSD subclasses.

	Neuropsychiatric disorders at any time point (n=60)					
	Any premorbid neuropsychiatric		**Mood Disorders**		**Neurotic Disorders**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
MND (ref)	-	-	-	-	-	-
MND-FTD	2.067	0.669 to 6.387	3.219	0.916 to 11.312	2.074	0.410 to 10.502
MNDbi	2.157	0.915 to 5.085	**3.923**	**1.511 to 10.187**	0.486	0.059 to 3.975
MNDci	0.794	0.254 to 2.480	1.207	0.322 to 4.535	1.315	0.450 to 3.839
MNDcbi	1.301	0.647 to 2.616	2.125	0.932 to 4.845	0.556	0.068 to 4.562

Results in bold indicate a significant association.

The relationship between patients' history of neuropsychiatric medication and their cognition and behaviour

Of the 305 patients with ECAS data on the CARE-MND register, 127 had a relevant neuropsychiatric medication in their medical history (92 antidepressants, 54 benzodiazepines and 5 antipsychotics). Based on date of medication prescription and date of MND diagnosis, 25 people were identified with premorbid neuropsychiatric medication (57 were prescribed post-MND diagnosis and 45 missing dates). There were no significant differences between those with premorbid neuropsychiatric medication and those without on demographic or disease characteristics.

We found no associations between the prescription of any neuropsychiatric medication and cognition and/or behaviour changes (supplementary eTable 4), MND-FTSD subclass

(supplementary eTable 5) or behaviour or cognitive impairment (eFigure 2). All results remained non-significant when including only those with medication prescribed prior to MND diagnosis (supplementary eTable 6-7 and eFigure1b).

The relationship between patients' family history of neuropsychiatric disorders and their cognition and behaviour

Of the 305 people with ECAS data on the CARE-MND register, information on family history of neuropsychiatric disorders was available for 231 (75.74%) patients. Patients with and without a family history of neuropsychiatric disorders did not differ on C9orf72 status (x^2=3.209, p=0.073). A positive family history of any neuropsychiatric disorder was present in 36/231 (15.58%). Mood disorders was the most common (n=16) followed by schizophrenia, schizotypal or delusional disorders (n=10) and neurotic disorders (n=9, Table 3). A positive family history of dementia was reported in 76/266 (29%, data unavailable for 39) as was associated with increased odds of a family history of neuropsychiatric disorders (OR=4.198, 95%CI=1.996 to 8.958). There were no other differences between those with and without a family history of neuropsychiatric disorders on demographic or disease characteristics.

A family history of any neuropsychiatric disorders was associated with poorer visuospatial scores. A family history of mood disorder was significantly associated with poorer total ECAS and ALS non-specific scores, as well as poorer language, verbal fluency and visuospatial scores. For a family history of neurotic disorders, we found an association with poorer language and visuospatial scores (Table 6). We did not find any other significant associations between family neuropsychiatric disorders and cognition or behaviour. After excluding MND-FTD cases, the association between family history of neurotic disorders and language scores remained (exp(B)=0.463, p=0.013). All other associations were no longer significant. All associations remained after controlling for C9orf72 status.

Table 6. Family history of neuropsychiatric disorders and cognitive and behavioural outcomes in patients.

	Any neuropsychiatric disorder		**Mood disorders**		**Neurotic disorders**		**Schizophrenia, schizotypal and delusional disorders**	
	exp(B)	***p***	**exp(B)**	***p***	**exp(B)**	***p***	**exp(B)**	***p***
Language	0.742	0.062	**0.574**	**0.021**	**0.362**	**<0.001***	0.845	0.522
Verbal Fluency	0.824	0.146	**0.634**	**0.023**	0.795	0.347	0.790	0.284
Executive functioning	0.965	0.755	0.891	0.504	0.815	0.329	0.878	0.489
ALS Specific	*0.864*	*0.167*	*0.739*	*0.054*	*0.717*	*0.093*	*0.854*	*0.375*
Memory	0.857	0.130	0.787	0.125	0.779	0.187	0.845	0.325
Visuospatial	**0.804**	**0.026**	**0.652**	**0.004**	**0.625**	**0.009**	0.812	0.201
ALS Non-specific	*0.820*	*0.058*	***0.696***	***0.018***	*0.720*	*0.091*	*0.799*	*0.199*
Total ECAS	*0.857*	*0.118*	***0.725***	***0.026***	*0.710*	*0.061*	*0.836*	*0.276*
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Disinhibition	0.352	0.019 to 1.879	<0.001	-	<0.001	-	<0.001	-
Apathy or inertia	2.059	0.883 to 4.705	2.248	0.620 to 7.839	5.455	0.027 to 3.698	1.560	-1.172 to 1.891
Loss of sympathy or empathy	0.858	0.236 to 2.487	0.532	0.028 to 2.967	<0.001	-	1.903	-1.316 to 2.176
Perseveration	2.026	0.721 to 5.237	1.241	0.182 to 5.195	1.104	-2.876 to 1.979	<0.001	-
Hyperorality or altered food preferences	1.903	0.632 to 5.140	2.606	0.538 to 9.883	1.291	-2.722 to 2.142	-0.909	-3.048 to 1.699

Results in bold indicate a significant association.

* Remained statistically significant following Bonferroni-Holm correction for multiple comparisons.

For MND-FTSD subclass, a family history of any neuropsychiatric disorder was associated with an increased risk of MND-FTD and MNDbi versus MND with no impairment. Examination of each neuropsychiatric disorder showed that a family history of mood and neurotic disorders were associated with an increased risk of MND-FTD versus MND with no impairment (Table 7).

The presence of any behaviour impairment was associated with a family history of any neuropsychiatric disorders or neurotic disorders (Figure 2b). We did not find any associations between family history of neuropsychiatric disorders and the presence of any cognitive impairment.

Table 7. Family history of neuropsychiatric disorders and MND-FTD subclass

	Any neuropsychiatric in family history		**Mood disorder**		**Neurotic disorder**		**Schizophrenia, schizotypal and delusional disorders**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
MND (ref)	-	-	-	-	-	-	-	-
MND-FTD	**5.077**	**1.263 to 20.403**	**7.571**	**1.555 to 46.867**	**13.750**	**1.705 to 110.861**	6.111	0.504 to 74.061
MNDbi	**3.136**	**1.094 to 8.989**	1.606	0.304 to 8.488	5.000	0.668 to 37.418	5.000	0.667 to 37.418
MNDci	1.202	0.484 to 2.988	0.841	0.203 to 3.482	0.846	0.075 to 9.515	3.548	0.632 to 19.929
MNDcbi	1.270	0.328 to 4.906	1.860	0.349 to 9.910	5.789	0.768 to 43.623	2.750	0.238 to 31.781

Results in bold indicate a significant association.

DISCUSSION

We showed that the associations between MND, FTD and neuropsychiatric disorders extend into the cognitive and behavioural features in MND. A premorbid mood disorder in an MND patient is associated with a 2.78 increase in the odds of apathy post-MND diagnosis and a family history of any neuropsychiatric disorder is associated with 3.14 and 5.08 increased odds of MNDbi and MND-FTD respectively. More specifically, a family history of mood disorder is associated with poorer overall cognition in addition to a 7.57 increase in the odds of MND-FTD. Patients with a family history of neurotic disorders are more likely to have poorer cognition, including language and visuospatial functioning, and a 13.75 increase in the odds of MND-FTD. These associations may contribute to the spectrum of cognitive and behavioural changes in MND.

Previous research has suggested that the C9orf72 expansion accounts for some of the shared predisposition between MND, FTD and neuropsychiatric disorders. In one study, C9orf72 was associated with higher rates of schizophrenia, suicide and autism in ALS and FTD family members.[32] Some studies have also shown an association between C9orf72 and cognition in ALS and FTD patients however these findings have been mixed.[33, 34] We showed that those with and without a personal or family history of neuropsychiatric disorders did not differ on C9orf72 status. To our knowledge, we are also the first to show that both patient and family neuropsychiatric history is associated with cognitive and behaviour changes in MND, independent of the patients C9orf72 status. These findings suggest that although a shared predisposition exists, factors other than C9orf72 status are contributing to this susceptibility. Furthermore, those with a premorbid neuropsychiatric disorder had a shorter disease duration at the time of ECAS assessment. This suggests that a neuropsychiatric history may be associated with poor cognition in the earlier stages of the disease however further research is needed to confirm this.

We showed associations across both ALS specific and non-specific cognitive domains. Although ALS non-specific, including visuospatial impairment, are less common in MND, different cognitive profiles exist and other factors may be contributing. Impaired visuospatial skills are common in Alzheimer's Disease (AD)[35] therefore our results may reflect the presence of mild AD pathology. Alternatively, visuospatial skills have been shown to decline with increasing disease stage, even in FTD[35] therefore it may be an effect of disease stage.

Many associations did appear to be driven by MND-FTD patients and were no longer significant after removal of these cases. However, a family history of neurotic disorders and language scores remained significant after the removal of MND-FTD cases showing that these associations exist in non-demented MND patients. Furthermore, many associations were found with MNDbi and more specific cognitive deficits suggesting that neuropsychiatric history is associated with the full spectrum of cognitive and behavioural changes in MND. Future research using more in-depth measures of neuropsychiatric disorders, including subclinical symptoms, may be more sensitive and reveal further associations.

We were able to identify cases of premorbid neuropsychiatric disorders in MND patients using diagnosis date and found a strong relationship between premorbid mood disorders and apathy post-MND diagnosis. These findings suggest that a history of mood disorders may be a risk factor for the development of apathy in MND. Apathy or demotivation is the most common behavioural impairment in ALS.[36, 37] Although some symptoms of depression and apathy may overlap, a dissociation in ALS has been demonstrated[37] and the distinct profile of initiation apathy found in ALS has been related to a cognitive failure to initiate as demonstrated by verbal fluency deficits.[38] Early signs of apathy may have been captured as premorbid mood disorders on the CARE-MND platform. Little is known about timing of cognitive and behavioural symptoms relative to motor symptom onset in MND. However, these are likely to be mood disorders as only 7/28 (25%) cases were diagnosed with mood disorders in the 5 years prior to MND diagnosis.

Associations between neuropsychiatric history and later-life disease have previously been demonstrated. An increased risk of dementia has been associated with a history of depression, anxiety, bipolar, schizophrenia and alcohol dependence.[39] Parkinson's Disease has also been associated with premorbid depression.[40] However, few studies have explored how premorbid neuropsychiatric disorders relate to cognitive and behavioural changes in neurodegenerative disease, including MND. The findings from this study highlight the contribution of neuropsychiatric symptoms to the cognitive and behavioural profiles in MND.

Our population-based study includes all MND patients in Scotland with cognitive and/or behavioural information assessed using the ECAS. This information allowed us to group

patients using established cut-offs and the latest ALS-FTSD classifications.[3, 20] Rates of cognitive and/or behavioural impairment in our sample (156/305, 51.1%) were consistent with previous research.[1] We identified cases of MND-FTD based on neurologist diagnosis therefore they may not be in strict adherence to the ALS-FTSD criteria.[3] This may have contributed to fewer cases being identified than in previous research; however our rates (17/305, 5.57%) were comparable to published frequencies.[41] A classification of MND-FTD cannot be made using ECAS data available on the CARE-MND platform as information indicating progression of cognitive and/or behavioural symptoms, a key criterion, is unavailable. Based on the other two MND-FTD criteria[3] an additional 23 patients may have MND-FTD, however this could not be confirmed. The ECAS is generally administered shortly following diagnosis; however changes in cognition and behaviour have been shown to increase in the final stages of the disease[29] therefore some patients may go on to develop MND-FTD.

Neuropsychiatric disorders were uncommon in the MND kindreds included in our study. We identified mood disorders in 42 (13.77%) patients and 28 (9.18%) family members which is lower than expected based on previous research[14, 15] and rates found in the UK Biobank (27.20% of 123,000).[42] This resulted in small numbers in some analyses therefore these results should be interpreted cautiously. We were unable to examine associations with psychosis, schizophrenia or autism, neuropsychiatric disorders which have been shown to occur at higher rates in MND kindreds.[11, 14, 15] The number of patients with neuropsychiatric medication was higher than those with a neuropsychiatric history (127 vs 60). Information on the duration and reason for neuropsychiatric medication use was not available on the CARE-MND register. Therefore, cases were neuropsychiatric medication was prescribed to treat short-term symptoms not meeting diagnostic criteria or non-neuropsychiatric symptoms (e.g. Duloxetine to treat fibromyalgia) may be been included. This may have contributed to the lack of associations found.

We used patient-reported family history data which may have contributed to the lower rates of neuropsychiatric disorders. The social stigma around mental health may prevent the sharing of this information and social and behavioural difficulties may lead to a loss of contact with family members. Furthermore 74/305 (24.26%) patients did not have any family history information. We may also have missed patient cases of neuropsychiatric disorders as we were unable to capture those: with subclinical symptoms not meeting traditional

diagnostic criteria; without an official diagnosis; who did not seek medical treatment; with previously under recognised disorders (i.e. autism spectrum disorders). Future research using more comprehensive and complete family and patient data may reveal stronger associations.

C9orf72 status was available for 259 (85%) patients in this study, allowing us to account for this in secondary analysis. Although we showed that almost all associations between patient and family neuropsychiatric history, and cognition and behaviour remained after controlling for the patients C9orf72 status, we did not control for any other factors. Future studies may also include other confounding variables and other genes or whole genome sequencing previously associated with cognitive and behavioural impairment.[41] Furthermore, future research should include other patient groups and healthy controls to determine whether these associations are specific to MND.

Finally, we focused on results unadjusted for multiple comparisons increasing the risk of a false-positive result. This study is experimental and hypothesis generating therefore it is important to show unadjusted effects as these warrant further examination in future research.[43] However, unadjusted findings should be interpreted with caution.

CONCLUSION

This is the first study to show that neuropsychiatric disorders in patients (premorbidly) and their family members are associated with cognitive and behavioural changes in MND. These associations were evident in those with premorbid neuropsychiatric disorders, without concurrent FTD and remained after accounting for C9orf72 status. These results provide further evidence of an overlap between MND, FTD and neuropsychiatric disorders and highlight the importance of further, large-scale studies, using more in-depth measurement of neuropsychiatric disorders and family history.

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eTable 1. Neuropsychiatric medications on the register and their class.

Drug Name	Class	Used to treat
Fluoxetine	SSRI	Depression, OCD, bulimia and panic disorders.
Citalopram	SSRI	Depression, panic disorder, agoraphobia and OCD.
Sertraline	SSRI	Depression, panic attacks, OCD and PTSD.
Duloxetine	SSRI	Depression, GAD and fibromyalgia.
Paroxetine	SSRI	Depression, OCD, social anxiety, panic disorder, PTSD and GAD.
Escitalopram	SSRI	Depression.
Amitriptyline	TCA	Depression, anxiety disorders, ADHD and bipolar disorder.
Clomipramine	TCA	OCD, panic disorder and depression.
Imipramine	TCA	Depression.
Nortriptyline	TCA	Depression.
Venlafaxine	SNRI	Depression, GAD, panic disorder and social phobia.
Mirtazapine	NaSSA	Depression, anxiety and insomnia.
Trazodone	SARI	Depression and anxiety.
Clonazepam	Benzodiazepine	Anxiety, seizure disorders and panic disorder.
Diazepam	Benzodiazepine	Anxiety and alcohol withdrawal.
Lorazepam	Benzodiazepine	Anxiety disorders, insomnia, active seizures and alcohol withdrawal.
Temazepam	Benzodiazepine	Anxiety and insomnia.
Olanzapine	Antipsychotic	Schizophrenia and bipolar disorder.
Risperidone	Antipsychotic	Schizophrenia, bipolar disorder and irritability in people with Autism.
Quetiapine	Antipsychotic	Schizophrenia, bipolar disorder and Depression.
Lithium	Anti-manic	Depression and bipolar disorder.
Naltrexone		Alcohol dependence and opioid dependence.

SSRI=Selective serotonin reuptake inhibitors; TCA=Tricyclic anti-depressant; SNRI=Serotonin and norepinephrine reuptake inhibitors; NaSSA=Noradrenergic and specific serotonergic antidepressant; SARI=Serotonin antagonist and reuptake inhibitors; OCD=Obsessive-Compulsive Disorder; PTSD=Post-traumatic stress disorder; GAD=Generalised anxiety disorder; ADHD=Attention deficit hyperactivity disorder.

eTable 2. Premorbid depression and anxiety associations with ECAS cognitive and behaviour scores.

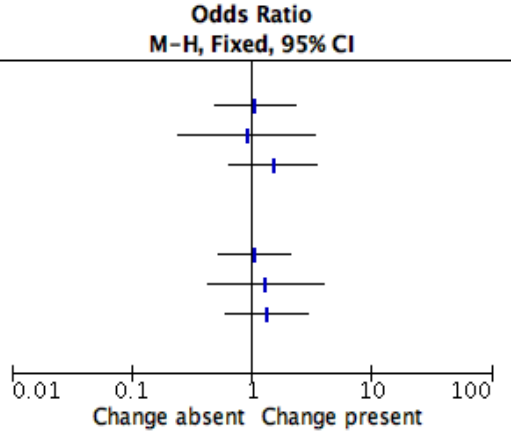
	Premorbid Neuropsychiatric Disorders Only (n=39)					
	Any neuropsychiatric disorder		**Mood Disorder**		**Neurotic Disorder**	
	exp(B)	***p***	**exp(B)**	***p***	**exp(B)**	***p***
Language	0.882	0.373	0.777	0.123	1.095	0.699
Verbal Fluency	0.916	0.480	0.904	0.491	0.883	0.563
Executive functioning	0.905	0.346	0.908	0.434	1.116	0.544
ALS Specific	*0.903*	*0.320*	*0.893*	*0.346*	*1.075*	*0.681*
Memory	0.889	0.201	0.841	0.109	0.905	0.530
Visuospatial	0.976	0.798	0.939	0.559	1.146	0.381
ALS Non-specific	*0.902*	*0.275*	*0.852*	*0.147*	*0.959*	*0.798*
Total ECAS	*0.901*	*0.256*	*0.879*	*0.233*	*1.038*	*0.815*
Total number of behaviour domains	1.180	0.167	1.163	0.264	0.984	0.941
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Disinhibition	1.153	0.257 to 3.729	0.961	0.146 to 3.676	<0.001	-
Apathy or inertia	2.009	0.848 to 4.647	**2.784**	**1.083 to 7.169**	1.914	0.368 to 8.937
Loss of sympathy or empathy	0.732	0.205 to 2.057	0.715	0.161 to 2.267	0.687	0.036 to 4.181
Perseveration	1.344	0.422 to 3.624	1.405	0.382 to 4.161	0.901	0.047 to 5.521
Hyperorality or altered food preferences	0.683	0.155 to 2.124	0.959	0.215 to 3.079	0.906	0.047 to 5.553

Results in bold indicate a significant association.

eFigure 1. Risk of any cognitive (MNDci, MNDcbi or MND-FTD) or behavioural (MNDbi, MNDcbi or MND-FTD) impairment – Premorbid cases.

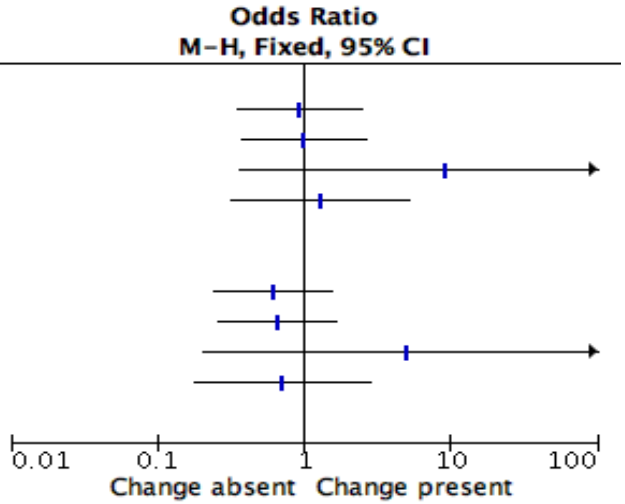
a) Premorbid Patient Neuropsychiatric Disorders

Study or Subgroup	+ve history neuropsych Events	Total	-ve history neuropsych Events	Total	Odds Ratio M-H, Fixed, 95% CI
4.3.1 Any behaviour impairment					
Any Psychiatric disorder - Behaviour	10	39	60	245	1.06 [0.49, 2.31]
Neurotic disorders - Behaviour	3	13	67	271	0.91 [0.24, 3.42]
Mood disorder - Behaviour	9	28	61	256	1.51 [0.65, 3.52]
4.3.2 Any cognitive impairment					
Any Psychiatric disorder - Cognition	16	39	98	245	1.04 [0.52, 2.07]
Neurotic disorders - Cognition	6	13	108	271	1.29 [0.42, 3.95]
Mood disorder - Cognition	13	28	101	256	1.33 [0.61, 2.91]



b) Premorbid Patient Neuropsychiatric Medication

Study or Subgroup	Medication Events	Total	No medication Events	Total	Odds Ratio M-H, Fixed, 95% CI
4.4.1 Any behaviour impairment					
Any medication - Behaviour	6	25	45	178	0.93 [0.35, 2.48]
Antidepressants - Behaviour	6	24	45	179	0.99 [0.37, 2.65]
Antipsychotics - Behaviour	1	1	50	202	9.06 [0.36, 225.92]
Benzodiazepine - Behaviour	3	10	48	193	1.29 [0.32, 5.20]
4.4.2 Any cognitive impairment					
Any medication - Cognition	7	25	69	178	0.61 [0.24, 1.55]
Antidepressants - Cognition	7	24	69	179	0.66 [0.26, 1.66]
Antipsychotics - Cognition	1	1	75	202	5.07 [0.20, 125.94]
Benzodiazepine - Cognition	3	10	73	193	0.70 [0.18, 2.81]



eTable 3. Premorbid patient neuropsychiatric disorders and MND-FTSD subclasses.

	Premorbid Neuropsychiatric disorders only (n=39)					
	Any premorbid neuropsychiatric		Mood Disorder		Neurotic Disorder	
	OR	95% CI	OR	95% CI	OR	95% CI
MND (ref)	-	-	-	-	-	-
MND-FTD	1.148	0.237 to 5.555	2.200	0.431 to 11.219	1.744	0.195 to 15.613
MNDbi	1.498	0.505 to 4.437	2.870	0.898 to 9.165	0.840	0.097 to 7.257
MNDci	0.827	0.226 to 3.020	1.015	0.210 to 4.907	1.333	0.364 to 4.884
MNDcbi	1.242	0.552 to 2.793	1.886	0.730 to 4.872	0.840	0.097 to 7.257

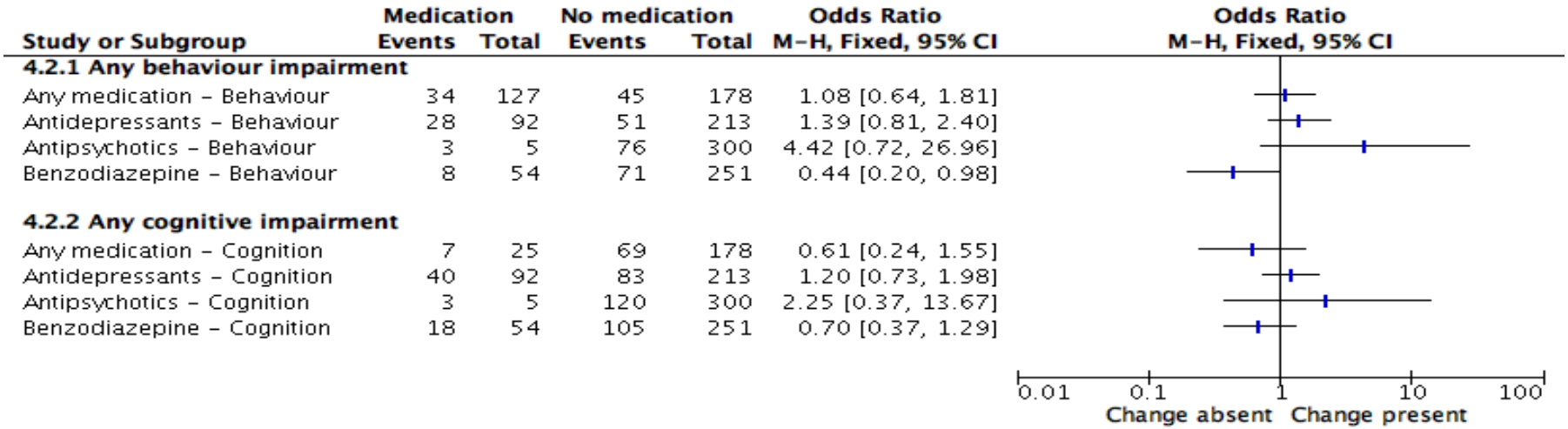
eTable 4. Patient neuropsychiatric medication associations with ECAS cognitive and behavioural scores.

	Any neuropsychiatric medication (n=127)							
	Any neuropsychiatric disorder		**Anti-depressants**		**Benzodiazepines**		**Anti-psychotics**	
	exp(B)	***p***	**exp(B)**	***p***	**exp(B)**	***p***	**exp(B)**	***p***
Language	0.889	0.225	0.935	0.529	1.086	0.515	0.578	0.133
Verbal Fluency	0.921	0.334	0.928	0.417	1.171	0.153	0.887	0.707
Executive functioning	1.022	0.767	1.025	0.750	1.039	0.687	0.741	0.265
ALS Specific	*0.975*	*0.717*	*0.981*	*0.805*	*1.088*	*0.354*	*0.749*	*0.273*
Memory	0.982	0.772	0.988	0.860	1.032	0.692	0.660	0.070
Visuospatial	0.939	0.331	0.979	0.758	0.963	0.657	1.355	0.209
ALS Non-specific	*0.980*	*0.755*	0.998	0.974	1.043	0.613	0.699	0.131
Total ECAS	*0.980*	*0.748*	*0.987*	*0.843*	*1.096*	*0.262*	*0.719*	*0.163*
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Disinhibition	0.868	0.364 to 1.980	0.541	0.175 to 1.399	0.532	0.122 to 1.626	2.667	0.129 to 21.744
Apathy or inertia	0.901	0.502 to 1.599	1.233	0.661 to 2.265	0.480	0.197 to 1.051	7.385	0.927 to 150.789
Loss of sympathy or empathy	1.071	0.554 to 2.045	0.923	0.439 to 1.853	0.570	0.205 to 1.356	3.978	0.467 to 33.891
Perseveration	0.891	0.422 to 1.831	1.278	0.581 to 2.693	0.654	0.212 to 1.663	5.588	0.653 to 47.875
Hyperorality or altered food preferences	0.834	0.397 to 1.703	0.877	0.382 to 1.880	0.633	0.206 to 1.608	1.750	0.085 to 14.105

eTable 5. Patient neuropsychiatric medication and MND-FTSD subclass.

	Neuropsychiatric medication at any time point (n=127)							
	Any neuropsychiatric medication		Anti-depressants		Benzodiazepines		Anti-psychotics	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
MND (ref)	-	-	-	-	-	-	-	-
MND-FTD	1.130	0.407 to 3.136	1.538	0.533 to 4.439	<0.001	-	9.250	0.552 to 155.091
MNDbi	1.519	0.712 to 3.243	1.833	0.834 to 4.032	0.680	0.242 to 1.905	4.625	0.282 to 75.906
MNDci	1.417	0.812 to 2.472	1.356	0.744 to 2.473	0.921	0.462 to 1.834	1.947	0.120 to 31.565
MNDcbi	0.986	0.435 to 2.239	1.269	0.533 to 3.022	0.439	0.125 to 1.547	5.286	0.321 to 87.016

eFigure 2 Risk of any cognitive (MNDci, MNDcbi or MND-FTD) or behavioural (MNDbi, MNDcbi or MND-FTD) impairment by patient neuropsychiatric medication for all identified cases.



eTable 6. Patient premorbid neuropsychiatric medication associations with ECAS cognitive and behavioural scores.

	Premorbid neuropsychiatric medication only (n=25)							
	Any neuropsychiatric disorder		**Anti-depressants**		**Benzodiazepines**		**Anti-psychotics**	
	exp(B)	***p***	**exp(B)**	***p***	**exp(B)**	***p***	**exp(B)**	***p***
Language	0.859	0.382	0.849	0.358	0.735	0.241	0.545	0.432
Verbal Fluency	1.083	0.622	1.041	0.808	1.298	0.282	1.336	0.684
Executive functioning	1.073	0.591	1.003	0.514	0.970	0.878	0.770	0.653
ALS Specific	*0.955*	*0.726*	*0.958*	*0.746*	*0.982*	*0.925*	*1.135*	*0.827*
Memory	0.989	0.926	0.953	0.683	0.834	0.293	0.527	0.206
Visuospatial	1.055	0.646	1.042	0.728	0.928	0.670	1.308	0.601
ALS Non-specific	*1.000*	*0.999*	0.961	0.743	0.845	0.346	0.557	0.263
Total ECAS	*1.017*	*0.875*	*1.003*	*0.981*	*0.976*	*0.879*	*0.771*	*0.584*
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Disinhibition	<0.001	-	<0.001	-	<0.001	-	<0.001	-
Apathy or inertia	0.810	0.249 to 2.275	0.882	0.269 to 2.508	0.765	0.109 to 3.472	<0.001	-
Loss of sympathy or empathy	0.466	0.071 to 1.763	0.500	0.076 to 1.903	1.457	0.206 to 6.730	<0.001	-
Perseveration	0.283	0.015 to 1.485	0.302	0.016 to 1.594	0.799	0.042 to 4.809	<0.001	-
Hyperorality or altered food preferences	0.268	0.015 to 1.404	0.286	0.016 to 1.507	0.758	0.040 to 4.551	<0.001	-

eTable 7. Patient premorbid neuropsychiatric medication and MND-FTSD subclass.

	Premorbid Neuropsychiatric medication only (n=25)							
	Any premorbid neuropsychiatric medication		Anti-depressants		Benzodiazepines		Anti-psychotics	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
MND (ref)	-	-	-	-	-	-	-	-
MND-FTD	<0.001	-	<0.001	-	<0.001	-	<0.001	-
MNDbi	1.082	0.282 to 4.147	1.172	0.304 to 4.521	0.886	0.101 to 7.783	<0.001	-
MNDci	0.598	0.187 to 1.914	0.648	0.201 to 2.089	0.383	0.045 to 3.273	<0.001	-
MNDcbi	1.022	0.268 to 3.898	1.107	0.289 to 4.250	1.772	0.332 to 9.447	<0.001	-